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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,449	12/20/2001	Monica G. Marcu	213373	4132

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EXAMINER	
LE, EMILY M	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,449	MARCU ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/20/2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-17 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-17 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claim(s)

1. Claims 2, 18-21 and 23 are cancelled. Claims 1, 3-17 and 22 are pending and under examination.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claim 1, 8-15 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Omarbasha et al.[1] as evidenced by Prodromou et al.[2]

In response to the rejection set forth in the previous office action, Applicant argues that Omarbasha et al. does not teach the invention as claimed for Omarbasha et al. teaches the administration of coumarin to a mammal only, Omarbasha et al. does not teach that the administered coumarin contacted Hsp90.

Applicant's submission has been considered, however, it is not found persuasive. In the instant, the teaching of Omarbasha et al. is comparable to those that are provided in Applicant's disclosure. In the specification submitted at the filing of the instant patent application, Applicant discloses that the contacting of coumarin with the chaperone protein can be carried out in any suitable manner, wherein one of which include the in

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[1] Omarbasha et al. Effect of coumarin on the Normal Rat Prostate and on the R-3327H prostatic adenocarcinoma. Cancer Research, 1989, Vol. 49, 3045-3049.

[2] Prodromou et al. Identification and structural characterization of the ATP/ADP-binding site in the Hsp90 molecular chaperone. Cell, 1997, Vol. 90, 65-75.

vivo administration of the coumarin to the mammal. In the instant, Omarbasha et al. teaches an in vivo administration of the coumarin to a mammal; ergo, Omarbasha et al. teaches the contacting of coumarin with the chaperone protein. Hence, Omarbasha et al. anticipates the claimed invention.

Also, it appears that Applicant is submitting that the instant specification is not enabling for the claimed invention. As stated above, Applicant argues that the administration of coumarin to mammal does not inherently result in a contact between coumarin and the Hsp90 protein. This argument is contradictory to the disclosure that is provided by Applicant. The disclosure sets forth that contacts between the coumarin and the Hsp90 protein can be ascertained by the administration of the coumarin to the mammal.

Furthermore, Applicant is reminded that reciting the mechanism of action of an old process doesn't make it a different process. In the instant, the claims recite a mechanism of action of an old process. The mechanism of action is contacting coumarin with Hsp90. And the old process is the administration of coumarin to a mammal. The recitation or discovery of a mechanism of action for an old process does not make it a different process; ergo, the discovery would not render an old process patentable.

4. Claim 1, 3, 5-15 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Eder et al.[3], as evidenced by Prodromou et al.

[3] Eder et al. Effect of novobiocin on the antitumor activity and tumor cell and bone marrow survivals of three alkylating agents. Cancer Research, 1989, Vol. 49, Issue 3, 595-598.

In response to the rejection set forth in the previous office action, Applicant submits that Eder et al. does not teach or suggest that novobiocin alone is administered so as to be localized near Hsp90, let alone that is administered so as to contact Hsp90 in order to inhibit binding of Hsp90 to its client protein/polypeptide.

Applicant's submission has been considered, however, it is not found persuasive. In the instant, the teaching of Eder et al. is comparable to those provided in Applicant's disclosure. In the specification submitted at the filing of the instant patent application, Applicant discloses that the contacting of coumarin with the chaperone protein can be carried out in any suitable manner, wherein one of which include the in vivo administration of the coumarin to the mammal. In the instant, Eder et al. teaches an in vivo administration of the coumarin to a mammal; ergo, Eder et al. teaches the contacting of coumarin with the chaperone protein. Hence, Eder et al. anticipates the claimed invention.

Also, it appears that Applicant is submitting that the instant specification is not enabling for the claimed invention. As stated above, Applicant argues that the administration of coumarin to mammal does not inherently result in a contact between coumarin and the Hsp90 protein. This argument is contradictory to the disclosure that is provided by Applicant. The disclosure sets forth that contacts between the coumarin and the Hsp90 protein can be ascertained by the administration of the coumarin to the mammal.

Additionally, Applicant is reminded that the claims recite the transitional term "comprising". The term "comprising" is inclusive or open-ended and does not exclude

additional, unrecited elements or method steps. Thus, Eder et al. does not have to administer the coumarin by itself to a mammal to anticipate the claimed invention.

Furthermore, Applicant is reminded that reciting the mechanism of action of an old process doesn't make it a different process. In the instant, the claims recite a mechanism of action of an old process. The mechanism of action is contacting coumarin with Hsp90. And the old process is the administration of coumarin to a mammal. The recitation or discovery of a mechanism of action for an old process does not make it a different process; ergo, the discovery would not render an old process patentable.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 3-6, 12-15 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al.,[4] in view of Gormley et al., [5] and Prodromou et al.

In response to the rejection set forth in the previous office action, Applicant submits that the Office's conclusion of obviousness is based only on the impermissible hindsight, and that the references relied upon by the Office do not provide any suggestion or motivation to combine the teachings thereof.

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[4] Schneider et al. Pharmacologic shifting of a balance between protein refolding and degradation mediated by Hsp90. Proc. Natl. Acad. Sci. 1996, Vol. 93, 14536-14541.

Applicant's submission has been considered, however, it is not found persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case:

In the instant, the motivation is clearly provided by Prodromou et al. Prodromou et al. teaches that the Hsp90 protein is a chaperone for a wide range of client proteins, wherein the client proteins are involved in cell proliferation and tumor progression. Thus, the inhibition of binding between the Hsp90 protein and its client protein would interfere with cellular proliferation and tumor progression. Hence, it would have been

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[5] Gormley et al. The interaction of coumarin antibiotics with fragments of the DNA gyrase B protein. Biochemistry, 1996, Vol. 35, 5083-5092.

prima facie obvious for one of ordinary skill in the art to inhibit the binding between Hsp90 protein and its client proteins. One of ordinary skill in the art at the time the invention was made would be motivated to do so to modulate cell proliferation and tumor progression.

One of ordinary skill in the art would have had a reasonable expectation of success for doing so because the references teach that the coumarin binding site on Hsp90 protein is homologous to that of geldanamycin. And the binding of geldanamycin to the Hsp90 protein, leads to the inhibition of binding between the Hsp90 protein and its client proteins.

7. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider, Prodromou, and Gormley et al., and in further view of Schulte et al.[6]

In response to the rejection set forth in the previous office action, Applicant submits that Schulte et al. does not bridge the gap between the claimed invention and Schneider et al., Gormley et al., and Prodromou et al. as discussed above.

Applicant's submission has been considered, however, it is not found persuasive. The significance of Schneider, Prodromou and Gormley et al. is provided above.

In the instant, the only gap present between what is instantly claimed and the combined teachings of Schneider, Prodromou and Gormley et al. is that the references do not teach the inhibition of client proteins such as serine/threonine Raf-1, tyrosine kinase $p185^{erbB2}$, and mutant p-53 with the chaperone protein.

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[6] Schulte et al. Geldanamycin-induced Destabilization of Raf-1 involves the Proteasome. Biochemical and Biophysical Research Communications, 1997, Vol. 239, 655-659.

However, the deficiency that is noted for the references is compensated by the teaching of Schulte et al.

Schulte et al. teaches that the binding of geldnamycin to the Hsp90 protein results in an inhibition of binding between the Hsp90 protein and its client proteins, such as serine/threonine Raf-1, tyrosine kinase $p185^{erbB2}$, and mutant p-53.

The teaching provided by Schulte et al. affirms the inherent property that is the result of binding geldnamycin to the Hsp90 protein. In the instant, since the binding site for geldanamycin on Hsp90 is the same as that of the ATP-binding site on Hsp90. This binding site is homologous to the ATP-binding site of DNA gyrase B protein. And the ATP-binding site of DNA gyrase B protein is also the binding site for coumarin and coumarin derivatives. Ergo, the binding of coumarin to Hsp90 would necessarily inhibit the binding of Hsp90 to serine/threonine Raf-1, tyrosine kinase p185 erbB2, and mutant p-53.

8. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Schneider, Prodromou, and Gormley et al. in further view of Hu et al.[7]

In response to the rejection set forth in the previous office action, Applicant submits that Hu et al., alone or in combination with the other references does not cure the deficiencies of the cited art. There is not teaching or suggestion in Hu et al. that contacting Hsp90 with coumarin or a coumarin derivative would inhibit the activity of hepatitis B virus reverse transcriptase.

Applicant's submission has been considered, however, it is not found persuasive.

[7] Hu et al. Hsp90 is required for the activity of a hepatitis B virus reverse transcriptase. Proc. Natl. Acad. Sci. USA, 1996, Vol. 93, 1060-1064.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case:

The significance of Schneider, Prodromou and Gormley et al. is provided above.

In the instant, the only deficiency that is noted of Schneider, Prodromou, and Gormley et al. is that the references do not teach the inhibition of hepatitis B virus by contacting the coumarin with the Hsp90 protein.

However, the deficiency noted for the references is compensated by the teaching of Hu et al.

Hu et al. teaches that Hsp90 is required for the activity of hepatitis B virus reverse transcriptase. Hu et al. teaches that reverse transcription in the virus is initiated by a protein-priming mechanism, wherein the viral encoded reverse transcriptase binds to a short RNA sequence and initiates DNA synthesis *de novo* by using a tyrosine residue within the polymerase polypeptide as the primer. Hu et al. also teaches that polymerase activation is dependent on ATP hydrolysis. Thus, without polymerase activation, the virus cannot replicate.

Gormley et al. teaches that ATP-hydrolysis is inhibited by binding coumarin and its derivatives to the ATP-binding domain of gyrase B protein.

Prodromou et al. teaches that the ATP-binding domain of gyrase B protein and ATP-binding domain of Hsp90 are homologous to one another.

Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Schneider, Prodromou, Gormley et al. and Hu et al. to inhibit hepatitis B viral replication.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because polymerase activation is dependent on ATP hydrolysis, which is inhibited by binding coumarin and its derivatives to the ATP-binding domain of gyrase B protein, which is homologous to ATP-binding domain of Hsp90.

Conclusion

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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